REMARKS

Claims 29, 30, and 32-35 are pending. No claims are allowed.

Claims 29, 30, and 32-35 have been amended to overcome 35 U.S.C. 112, second paragraph, issues raised by the Examiner.

Claims 29 and 30 have also been amended to limit the size of the antigens used to make the polyclonal or monoclonal antibodies to the antigens with molecular weights of 16 and 30 kDa as determined by the applicants by SDS polyacrylamide gel electrophoresis. Support for this amendment can be found on page 13, line 16, which incorporates by reference U.S. Serial No. 09/156,954, filed on September 18, 1998, now U.S. Patent 6,153,394 to Mansfield *et al*. The application discloses that by probing Western blots of *Sarcocystis neurona* antigens separated by SDS polyacrylamide gel electrophoresis with antisera from horses infected with *Sarcocystis neurona,* two unique antigens, a 16 (±4) antigen and a 30 (±4) kDa antigen, were identified.

1. Claims 29, 30, and 32-35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Liang *et al*.(1997) or Liang *et al*.(1998) or Granstrom *et al*.(1993) in view of Harlow and Lane.

The prior art does not render the applicants'

presently amended claims *prima facie* obvious. According to M.P.E.P. § 2143.01, "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The test for an implicit showing is what the combined teachings, the knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." M.P.E.P. § 2143.01 citing *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). In other words, the prior art must suggest the desirability of the claimed invention. "The level of skill cannot be relied upon to provide the suggestion to combine the references." M.P.E.P. § 2143.01 citing *Al-Site v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1162 (Fed. Cir. 1999). Thus, the motivation for combining the prior art references must either reside in the references or in the knowledge generally available to one of ordinary skill in the art.

In this case, neither Liang (1998), Liang (1997), nor Granstrom teaches, suggests, or provides any motivation to one of ordinary skill in the art to

combine it with Harlow and Lane to make the applicants' presently claimed method for producing polyclonal or monoclonal antibodies against the 16 and 30 kDa *Sarcocystis neurona* antigens. Thus, the issue turns on whether the general knowledge available to one of ordinary skill in the art would have taught, suggested, or motivated one of ordinary skill in the art to combine either Liang (1998), Liang (1997), or Granstrom with Harlow and Lane to produce the applicants' presently claimed method.

In rebuttal to the applicants' argument in Paper No. 5 explaining why the applicants believe the prior art does not render the applicants' claimed method *prima facie* obvious, Paper No. 6 suggests that it has become routine in recent years to produce antibodies to any given antigen or epitope. Campbell was cited in Paper No. 6 because of its statement that making monoclonal antibodies against proteins has become so routine that researchers will make monoclonal antibodies against a protein, even "without any clear objective" or "motivation" for doing so. Thus, Paper No. 6 appears to have taken the position that it is the general knowledge available to one of ordinary skill in the art that making antibodies is routine which would have provided the necessary teaching, suggestion, or motivation to combine either Liang (1998), Liang (1997), or Granstrom

with Harlow and Lane to make the applicants' claimed invention.

Generating antibodies to a given antigen or epitope may have become routine in recent years, but that merely reflects the level of general skill of one of ordinary skill in the art, that is, that the making of antibodies is no longer perceived as being technically complex or unduly time consuming. In general, that is insufficient to provide the necessary teaching, suggestion, or motivation to one of ordinary skill in the art to combine the prior art to produce the applicants' claimed invention. There must also be a clear objective or motivation for one skilled in the art to combine the prior art. Therefore, even though one of ordinary skill in the art would have generally known that antibodies would be useful in immunoassays and the like, for any particular case, there still must be some motivation to achieve a particular objective for one skilled in the art to combine the prior art. The particular objective has to be more than making antibodies merely because it may be routine. There must be some objective or motivation for doing so, either within the general knowledge available to one skilled in the art or within the prior art references themselves. In other words, one skilled in the art must have recognized either in the prior art or the general

knowledge available, a particular need for a method for making antibodies against the 16 and 30 kDa antigens of *Sarcocystis neurona*.

The Court in *In re Kotzab*, at 1317, stated that in the test for establishing an implicit teaching, motivation, or suggestion with respect to two isolated statements in a prior art reference, the "statements cannot be viewed in the abstract." The statements "must be considered in the context of the teaching of the entire reference." It is believed that the same rationale applies when establishing *prima facie* obviousness based on the general knowledge available to one skilled in the art. The general knowledge available to one skilled in the art must be considered in the context of the teachings of the prior art references to determine whether it would be able to provide the motivation to combine the prior art references. When the general knowledge available to one of ordinary skill art is viewed in the context of either Liang (1998), Liang (1997), or Granstrom, there is no motivation for one of ordinary skill in the art to combine the prior art reference with Harlow and Lane.

With respect to Liang (1998), the general knowledge available to one skilled in the art would not have been a sufficient motivating factor for combining Liang (1998) with Harlow and Lane. Liang (1998) is

concerned with identifying antigens which are involved in infection and immunity and thus, may be useful in a vaccine against *Sarcocystis neurona*. Liang (1998) can be construed as teaching away from making monoclonal antibodies against *Sarcocystis neurona* antigens by the statement that "[a]lthough monoclonal antibodies are often used to study parasitic proteins, the sera of naturally infected animals have unique advantages in that they can provide important information on protectively immunogenic proteins in the natural host." [page 1837, last para.] Liang (1998) says nothing about whether polyclonal antibodies would be useful or desirable. In fact, making antibodies of any kind against *Sarcocystis neurona* would not appear to be particularly useful in identifying antigens which would be useful in a vaccine. Thus, within the context of Liang (1998), there would have been no need for antibodies against the 16 and 30 kDa antigens. Therefore, because Liang (1998) is not concerned with making antibodies of any kind against any *Sarcocystis neurona* antigens and is not concerned with assays which would use antibodies to detect *Sarcocystis neurona* antigens or vaccines which would use such antibodies, there would have been no motivation for one of ordinary skill in the art to combine Liang (1998) with Harlow and Lane to arrive at the applicants' presently claimed

method even when the generally available knowledge that making antibodies is routine is taken into consideration.

With respect to Granstrom, Granstrom is concerned with identifying antigens which are specific to *Sarcocystis neurona* and which can be used in immunoassays for detecting *Sarcocystis neurona*-specific antibodies from horse sera with symptoms suggesting EPM. Granstrom identifies a number of *Sarcocystis neurona* antigens but does not identify either the 16 or the 30 kDa antigen. Therefore, within the context of Granstrom, one of ordinary skill in the art would not have divined from either Granstrom or the general knowledge available to one skilled in the art the suggestion or motivation to combine Granstrom with Harlow and Lane for the purpose of making antibodies against the 16 and 30 kDa antigens of *Sarcocystis neurona* as presently claimed by the applicants.

With respect to Liang (1997), the general knowledge available to one skilled in the art would not have been a motivating factor for combining Liang (1997) with Harlow and Lane. Liang (1997) is concerned with a method for purifying proteins from an organism such as *Sarcocystis neurona*. Liang (1997) is particularly concerned with a method for purifying proteins to a point where the proteins are suitable for

microsequencing. While Liang (1997) teaches that it sequenced the N-terminus of the purified *Sarcocystis neurona* antigens (19 and 30 kDa) and used a synthetic 20-mer peptide based on the sequence of one of the purified antigens to make polyclonal antibodies reactive with the original protein, the teaching merely demonstrates that the method can be used to purify proteins to a level of purity sufficient for microsequencing. Liang (1997) does not teach or suggest that there is any need for making antibodies against the 16 and 30 kDa antigens. Furthermore, Liang (1997) does not even identify a 16 kDa antigen. Therefore, within the context of Liang (1997), even though making antibodies against proteins may be routine, that alone would not have motivated one skilled in the art to combine Liang (1997) with Harlow and Lane for the purpose of making antibodies against the 30 kDa antigen and the 16 kDa antigen in particular as presently claimed by the applicants.

It appears that in this case, relying on the notion that making antibodies is routine to provide the motivation for combining either Liang (1998), Liang (1997), or Granstrom with Harlow and Lane to produce the applicants' claimed method is a hindsight rejection. The prior art references do not identify any need for making antibodies against the 16 and 30 kDa antigens or

identify any problem that the antibodies could be used to solve. The general knowledge that making antibodies against antigens is routine also does not identify any need for antibodies against the 16 and 30 kDa antigens or identify any problem which the antibodies could be used to solve. While it is generally known that antibodies are useful, within the context of any of the prior art, one of ordinary skill in the art would not have had any motivation to combine Liang (1998), Liang (1997), or Granstrom with Harlow and Lane for the purpose of making antibodies against the 16 and 30 kDa antigens. It is only after the applicants have made their antibodies and disclose their rationale for doing so that one in hindsight can apply the general knowledge of the apparent routine nature for making antibodies to establish a case for *prima facie* obviousness. The M.P.E.P. § 2142 states that "The tendency to resort to 'hindsight' based on the applicant's disclosure is often difficult to avoid due to the nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." Thus, the rejection appears to a hindsight rejection based on the applicants' disclosure which is impermissible.

In light of the above, presently amended Claims 29, 30, and 32-35 are not believed to be *prima*

facie obvious over Liang (1998), Liang (1997), or Granstrom in view of Harlow and Lane. Reconsideration of the rejection is requested.

2. Claims 29, 30, and 32-35 were rejected under 35 U.S.C. § 112, second paragraph.

The claims have been amended to address the issues raised by the Examiner.

Claim 29 in step (f) has been amended to recite "removing serum from the immunized mammal and isolating from the serum the antibodies against the . . . antigen . . . ." This amendment clarifies the process being performed in step (f).

Claim 29 in step (e) has been amended to recite "immunizing a mammal with the admixture containing the fusion polypeptide and the adjuvant to produce antibodies against the 16 kDa antigen or the 30 kDa antigen comprising the fusion polypeptide." Step (e) in Claim 30 was amended in a similar manner. The amendment clarifies that antibodies against the 16 and 30 kDa antigens are being made.

With respect to what the method in Claims 29 and 30 is producing, the applicants are claiming a method for producing an antibody against the 16 kDa antigen in a fusion polypeptide or the 30 kDa antigen in a fusion polypeptide. This should be clear from the

preamble which states a method for producing a polyclonal (Claim 29) or monoclonal (Claim 30) antibody against an antigen selected from the Markush group consisting of the 16 and 30 kDa antigens and the same Markush group in step (a).

Claims 32-35 have been amended to remove reference to cancelled Claim 31 and to include reference to Claim 29.

Claim 32 has also been amended to recite that the polypeptide comprising the fusion polypeptide is protein A and the isolation of the fusion polypeptide is by affinity chromatography using an IgG-linked resin which binds the protein A comprising the fusion polypeptide. Claims 33-35 were amended in a similar manner. The amendments clarify that the affinity chromatography uses the particular resin to isolate the fusion polypeptide.

In light of the above amendments to Claims 29, 30, and 32-35, the claims are now believed to be in suitable form for allowance. Reconsideration of the rejections is requested.

3. Claims 29, 30, and 32-35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mansfield *et al.* (U.S. Patent No. 6,153,394) in view of Harlow and Lane (Chapter 6 (1986)).

Mansfield *et al.* is not believed to be available as prior art against the applicant's invention. In this case, Mansfield *et al.* can only be available as prior art if it qualifies under 35 U.S.C. § 102(e). Mansfield *et al.* does not qualify as prior art under 35 U.S.C. § 102(a) because it was patented November 28, 2000, which was after the September 26, 2000, date the present application was filed and after the date of the parent application was filed. Because Mansfield *et al.* was filed before the present application was filed but was patented after the present application was filed, Mansfield *et al.*, can only be available as prior art under 35 U.S.C. § 102(e).

However, according to 35 U.S.C. § 103(c), subject matter that qualifies as prior art under § 102(e) shall not preclude patentability under 35 U.S.C. § 103 if the subject matter of the reference and the claimed invention were, at the time the invention was made, commonly owned. This benefit applies to applications filed after November 29, 1999. The present application was filed September 26, 2000, so 35 U.S.C. § 103(c) applies.

Mansfield *et al.* and the present application are commonly owned. Both the present invention at the time it was made and Mansfield *et al.* were under an obligation of assignment to the Board of Trustees

operating Michigan State University.

The present application is a divisional of Application Serial No. 09/513,086, filed February 24, 2000, and which claims priority via a Provisional Application to September 2, 1999. The assignment of the '086 application to the Board of Trustees operating Michigan State University was recorded in the U.S. Patent and Trademark Office on February 24, 2000, Reel/Frame: 010590/0486. The present application refers to the assignment of the '086 application in the New Application Transmittal Form. The assignment of Mansfield *et al.* to the Board of Trustees operating Michigan State University was recorded in the U.S. Patent and Trademark Office on September 18, 1998, Reel/Frame: 9476/0775. A copy of the Notice of Recordation and the assignment for the '086 application and Mansfield *et al.* are enclosed.

When Mansfield *et al.* is excluded as prior art, the applicants' invention is clearly not rendered *prima facie* obvious in view of Harlow and Lane. Therefore, Claims 29, 30, and 32-35 are not believed to be *prima facie* obvious. Reconsideration of the rejection is requested.

4. Claims 29, 30, and 32-35 were rejected under the judicially created doctrine of obviousness-type double

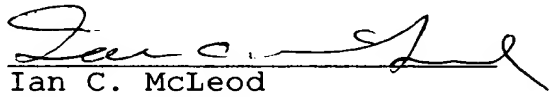
patenting as being unpatentable over Claims 1-36 (*See* Claims 21, 33, and 34) of U.S. Patent No. 6,344,337 ('337) to Mansfield in view of Harlow and Lane.

Mansfield and the present application are commonly owned. A terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) is being filed with this amendment. Reconsideration of the rejection is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

In light of the above, it is believed that Claims 29, 30, and 32-35 are in proper form for allowance. Notice of allowance is requested.

Respectfully,



Ian C. McLeod
Registration No. 20,931

MCLEOD & MOYNE, P.C.
2190 Commons Parkway
Okemos, MI 48864
(517) 347-4100
FAX (517) 347-4103

Encls.
(1) Terminal Disclaimer
(2) Notice of Recordation and assignment for U.S. Patent No. 6,153,394
(3) Notice of Recordation and assignment for Application Serial No. 09/513,086

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 29, 30, 32, 33, 34, and 35 were amended as follows.

-29- (Twice amended)

A method for producing an antibody against a *Sarcocystis neurona* antigen selected from the group consisting of a 16 [±4] kDa antigen and a 30 [±4] kDa antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising:

(a) providing a microorganism containing a DNA encoding a fusion polypeptide in which a *Sarcocystis neurona* antigen selected from the group consisting of the 16 [±4] kDa antigen and the 30 [±4] kDa antigen is fused to a polypeptide which enables isolation of the fusion polypeptide by affinity chromatography;

(b) culturing the microorganism in a culture to produce the fusion polypeptide from the DNA;

(c) isolating the fusion polypeptide from the culture by affinity chromatography;

(d) admixing the fusion polypeptide isolated by the affinity chromatography with an adjuvant to produce an admixture;

(e) immunizing a mammal with the admixture

containing the fusion polypeptide and the adjuvant [which causes the mammal] to produce antibodies against the 16 kDa antigen or the 30 kDa antigen comprising the fusion polypeptide; and

(f) removing serum from the immunized mammal and isolating [the antibodies] from the serum [to produce] the antibody against the *Sarcocystis neurona* antigen selected from the group consisting of the 16 [±4] kDa antigen and the 30 [±4] kDa antigen.

Sub D1

-30-(Twice amended)

A method for producing a monoclonal antibody against a *Sarcocystis neurona* antigen selected from the group consisting of a 16 [±4] kDa antigen and a 30 [±4] kDa antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising:

(a) providing a microorganism containing a DNA encoding a fusion polypeptide in which a *Sarcocystis neurona* antigen selected from the group consisting of the 16 [±4] kDa antigen and the 30 [±4] kDa antigen is fused to a polypeptide which enables isolation of the fusion polypeptide by affinity chromatography;

(b) culturing the microorganism in a culture to produce the fusion polypeptide from the DNA;

(c) isolating the fusion polypeptide from the culture by the affinity chromatography;

(d) admixing the fusion polypeptide isolated by the affinity chromatography with an adjuvant to produce an admixture;

(e) inoculating mice with the admixture containing the fusion polypeptide and the adjuvant [which causes the mice] to produce antibodies against the 16 kDa antigen or the 30 kDa antigen comprising the fusion polypeptide;

(f) removing the spleens from the mice which produce the antibodies against the fusion polypeptide;

(g) removing spleen cells from the spleens and mixing the spleen cells from the spleens with mouse myeloma cells to produce a mixture of fused cells consisting of spleen cells fused to myeloma cells, the spleen cells, and the myeloma cells;

(h) selecting the fused cells on cell culture medium in which the fused cells can grow but in which the spleen cells and the myeloma cells cannot grow; and

(i) screening the fused cells for fused cells which produce the monoclonal antibody against the *Sarcocystis neurona* antigen selected from the group consisting of the 16 [±4] kDa antigen and the 30 [±4] kDa antigen to produce the monoclonal antibody.

-32-(Twice amended)

The method of Claim [31] 29 or 30 wherein the polypeptide comprising the fusion polypeptide is protein A and the isolation of the fusion polypeptide is by affinity chromatography [comprises] using an IgG-linked resin which binds the protein A comprising the fusion polypeptide.

-33-(Twice amended)

The method of Claim [31] 29 or 30 wherein the polypeptide comprising the fusion polypeptide is polyhistidine and [the] isolation of the fusion polypeptide is by affinity chromatography [comprises] using a Ni^{2+} resin which binds the polyhistine comprising the fusion polypeptide.

-34-(Twice amended)

The method of Claim [31] 29 or 30 wherein the polypeptide comprising the fusion polypeptide is glutathione S-transferase and [the] isolation of the fusion polypeptide is by affinity chromatography [comprises] using a glutathione Sepharose 4B resin which binds the glutathione S-transferase comprising the fusion polypeptide.

The method of Claim [31] 29 or 30 wherein the polypeptide comprising the fusion polypeptide is a maltose binding protein and [the] isolation of the fusion polypeptide is by affinity chromatography [comprises] using an amylose resin which binds the maltose binding protein comprising the fusion polypeptide.